Docket No.: 066662-0092   **PATENT**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Palsson, Bernhard	Customer No.: 41552
Appl. No.	:	09/923,870	Confirmation No.: 1729
Filed	:	August 06, 2001	
Title	:	METHODS FOR IDENTIFYING DRUG TARGETS BASED ON GENOMIC SEQUENCE DATA	

Grp./A.U.   :   1647
Examiner: :   Allen, Marianne P.

DECLARATION UNDER 37 C.F.R. § 1.132

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jeremy S. Edwards, Ph.D., declare as follows:

1)   I am currently an Assistant Professor at the Department of Molecular Genetics and Microbiology at the University of New Mexico Health Science Center, Albuquerque, New Mexico. I previously held the Outstanding Junior Faculty Chaired Professorship position in Chemical Engineering at the University of Delaware.

2)   I obtained a Bachelors of Science majoring in Mechanical Engineering in 1995 from the University of Texas, Arlington and my Ph.D. in Bioengineering from the University of California, San Diego, in 1999, where I did my thesis work in Dr. Bernhard Palsson's laboratory. I also completed a post-doctoral fellowship at Harvard Medical School in 2000. I have authored or co-authored numerous papers in the areas of genomics and bioinformatics including *in silico* organism models, spatial-temporal modeling of signaling networks and functional genomics tool development. My curriculum vitae and a list of publications is attached as Exhibit 1.

3)   I have read the application entitled Methods for Identifying Drug Targets Based on Genomic Sequence Data, having U.S. patent application serial no. 09/923,870. Specifically, I understand that the application describes and claims computer methods for producing a genome specific stoichiometric matrix and computer methods for producing an *in silico* representation of a microbe. The methods rely, in part, on the identification and inclusion of metabolic reactions into an *in silico* model of an organism.

4)   I have read the Office Action mailed December 22, 2006, issued in connection with the above-identified application. I understand that claims 49 and 57 have been rejected for lacking written description in the application with respect to the phrase "a number of DNA sequences in a genome sufficient to produce an *in silico* representation of a microbe." In particular, I understand that the Examiner interprets the application to describe that most or all of the genes involved in metabolism should be included in an *in silico* representation and, therefore, concludes that the application fails to convey that including only a sufficient number was contemplated.

5)   My understanding from reading the application is that it sufficiently conveys that an *in silico* representation need only include a number of genes encoding metabolic reactions that is sufficient to produce a representation of an organism. This number of genes is far less than the most or all the genes involved metabolism as interpreted by the Examiner.

6)   Sufficiency can be assessed by a number of criteria described in the application and known to those skilled in the field of *in silico* modeling. In general, sufficiency is measured by consistency with *in vivo* results. The application adequately conveys this measurement when it explains "[t]he growth associated maintenance requirements are determined by fitting the model results to the experimentally determined points in the growth rate versus glucose rate plot" (page 8, lines 5-7; emphasis added). This conclusion is further born out by a comparison of *in silico* and *in vivo* results where the application explicitly describes "we can call upon the wealth of data on overall metabolic behavior and detailed biochemical information about the *in vivo* genotype to which we can compare the behavior of the *in silico* strain (page 14, last paragraph, lines 6-8; emphasis added).

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7)   The above descriptions convey to one skilled in the art of *in silico* modeling that sufficiency of the number of metabolic genes to include in an *in silico* representation can readily be determined by comparison with results obtained *in vivo*.

8)   I also understand the descriptions in the application directed to including most of the metabolic reactions or most or all of the genes involved in the organism's metabolism not to be a mandate for producing an *in silico* model. Rather, these descriptions refer to what could be desirable to include in the best working *in silico* model that can be constructed because a person skilled in the field of *in silico* modeling understands that increasing the number of reactions included in a model can increase the accuracy of the model.

9)   My understanding from reading the application with respect to the phrases "most or all of the genes" or "nearly the entire gene complement" is that these phrases describe that the methods described in the application have the power to be applied to organisms where little to no functional gene assignments have been made. This interpretation is clear when the cited phrase is read in context of the complete paragraph or sentence in the application. For example, the application describes that "the metabolic genotype of an organism includes 'most or all of the genes' involved in the organism's metabolism," but, as set forth below, conditions the number of genes on those that can be determined from the genomic sequence (paragraph bridging pages 7 and 8). The application also describes "[t]hus, the functions of nearly the entire gene complement or genotype of an organism can be determined so long as homologous genes have already been discovered" (page 7, second paragraph, last sentence; emphasis added). Thus, these passages, when read in context of the application, convey to one skilled in the field of *in silico* modeling the applicability of the described methods, not that the entire gene complement needs to be obtained to produce an *in silico* representation.

10)   With respect to the number of metabolic genes to include in an *in silico* representation, the application describes at page 7, second paragraph, lines 9-11, that if a coding region from a gene is homologous to a gene in a database then it is assigned a function. This statement clearly places a condition which limits including most or all of the metabolic genes of an organism in an *in silico* representation to those where homology can be assigned.

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11) The application further limits the number of genes that can be included in an *in silico* representation to less than all or most metabolic genes when it concludes "functions of nearly the entire gene complement or genotype of an organism <u>can</u> be determined <u>so long as homologous genes have already been discovered</u>" (page 7, second paragraph, lines 11-13; emphasis added). This statement conveys what can be done, not what is required, and clearly restricts the number of included metabolic genes because it was well understood that homologies for all metabolic genes were not known at the time this application was filed.

12) The application further describes that "[T]he gene products . . . carry out all or most of the enzymatic reactions . . . known to occur within the target organism <u>as determined from the genomic sequence</u>" (page 7, last line through page 8, line 3; emphasis added). Such description clearly conditions the number of genes to include in an *in silico* representation on how the information is acquired.
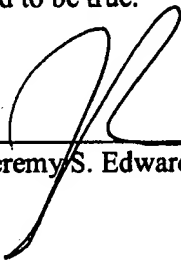
13) The above understanding is supported by a comparison of the *E. coli* model described in the application with models currently in use. The *E.coli* model described in the application was subsequently published by myself and Dr. Palsson and contained about 660 metabolic genes (Edwards et al., *Proc. Natl. Acad. Sci. USA* 97:5528-33 (2000). In comparison, the model I now use in my laboratory currently contains about 1,237 metabolic genes. The increase in gene number has resulted from the further identification of open reading frames that correspond to metabolic genes. Hence, the model described in the application contains only about half of the metabolic genes known today, but was sufficient to predict the behavior of an organism.

14) The above descriptions in the application convey that only a sufficient number of genes need to be obtained to produce an *in silico* representation and that not all or most metabolic genes will be included in an *in silico* representation because they condition the number of genes on what is known or how the information is acquired.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true.

Date: _06/07/07_   By: _____

Jeremy S. Edwards, Ph.D.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Jeremy S Edwards	POSITION TITLE Assistant Professor
eRA COMMONS USER NAME jedwards	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Texas, Arlington	B.S.	1995	Mech Eng
University of California, San Diego	M.S.	1997	Bioengineering
University of California, San Diego	Ph.D.	1999	Bioengineering

A. Positions and Honors

Positions and Employment
1999 - 2000	Postdoctoral Fellow, Department of Genetics, Harvard Medical School
1999 - 2005	Assistant Professor, Chemical Engineering, University of Delaware
2005-	Assistant Professor, Department of Molecular Genetics and Microbiology, University of New Mexico Health Sciences Center
2005-	Member, Cancer Research and Treatment Center, University of New Mexico Health Sciences Center
2005	Assistant Professor, Department of Chemical Engineering, University of New Mexico

Honors, Awards and Professional Memberships
1995   University of Texas, Arlington, Summa Cum Laude
2003-2004   Outstanding Named Junior Professor of Engineering
Member, American Association for the Advancement of Science (AAAS)
Member, American Society for Microbiology (ASM)
Member, American Institute or Chemical Engineers (AIChE)

B. Selected peer-reviewed publications
1. Edwards, J. S. & Palsson, B. O. How will bioinformatics influence metabolic engineering? *Biotechnology and Bioengineering* 58, 162-169 (1998).
2. Schilling, C. H., Edwards, J. S. & Palsson, B. O. Towards metabolic phenomics: Analysis of genomic data using flux balances. *Biotechnology Progress* 15, 288-95 (1999).
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4. Edwards, J. S. & Palsson, B. O. Systems Properties of the *Haemophilus influenzae* Rd Metabolic Genotype. *Journal of Biological Chemistry* 274, 17410-17416 (1999).
5. Schilling, C. H., Edwards, J. S., Letscher, D. & Palsson, B. O. Combining pathway analysis with flux balance analysis for the comprehensive study of metabolic systems. *Biotechnology and Bioengineering* 71, 286-306 (2000).
6. Edwards, J. S., Schilling, C. H., Covert, M. W., Smith, S. J. & Palsson, B. O. in *Encyclopedia of Microbiology* (ed. Lederberg, J.) (American Society for Microbiology, 2000).
7. Edwards, J. S. & Palsson, B. O. Metabolic flux balance analysis and the *in silico* analysis of *Escherichia coli* K-12 gene deletions. *BMC Bioinformatics* 1, 1 (2000).
8. Edwards, J. S. & Palsson, B. O. Robustness Analysis of the *Escherichia coli* metabolic network. *Biotechnol Prog* 16, 927-939 (2000).
9. Edwards, J. S. & Palsson, B. O. The *Escherichia coli* MG1655 in silico metabolic genotype: its definition, characteristics, and capabilities. *Proc Natl Acad Sci U S A* 97, 5528-33 (2000).
10. Edwards, J. S. & Palsson, B. O. Multiple steady states in kinetic models of red cell metabolism. *J Theor Biol* 207, 125-127 (2000).

11. Tchieu, J. H., Norris, V., Edwards, J. S. & Saier, M. H., Jr. The complete phosphotranferase system in *Escherichia coli. J Mol Microbiol Biotechnol* 3, 329-46. (2001).

12. Ramakrishna, R., Edwards, J. S., McCulloch, A. & Palsson, B. O. Flux-balance analysis of mitochondrial energy metabolism: consequences of systemic stoichiometric constraints. *Am J Physiol Regul Integr Comp Physiol* 280, R695-R704 (2001).

13. Jamshidi, N., Edwards, J. S., Fahland, T., Church, G. M. & Palsson, B. O. Dynamic simulation of the human red blood cell metabolic network. *Bioinformatics* 17, 286-7. (2001).

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15. Covert, M. W., Schilling, C. H., Famili, I., Edwards, J. S., Goryanin, I. I., Selkov, E. & Palsson, B. O. Metabolic Modeling of Microbial Strains *in silico. Trends Biochem Sci* 26, 179-86 (2001).

16. Badarinarayana, V., Estep, P. W., 3rd, Shendure, J., Edwards, J., Tavazoie, S., Lam, F. & Church, G. M. Selection analyses of insertional mutants using subgenic-resolution arrays. *Nat Biotechnol* 19, 1060-1065 (2001).

17. Schilling, C. H., Covert, M. W., Famili, I., Church, G. M., Edwards, J. S. & Palsson, B. O. Genome-scale metabolic model of *Helicobacter pylori* 26695. *J Bacteriology* 184, 4582-4593 (2002).

18. Papin, J. A., Price, N. D., Edwards, J. S. & Palsson, B. O. The genome-scale metabolic extreme pathway structure in *Haemophilus influenzae* shows significant network redundancy. *Journal of Theoretical Biology* 215, 67-82 (2002).

19. Mahadevan, R., Edwards, J. S. & Doyle, F. J., III. Dynamic Flux Balance Analysis of Diauxic Growth in *Escherichia coli. Biophys J* 83, 1331-1340 (2002).

20. Kauffman, K. J., Pajerowski, J. D., Jamshidi, N., Palsson, B. O. & Edwards, J. S. Description and analysis of metabolic connectivity and dynamics in the human red blood cell. *Biophys J* 83, 646-62 (2002).

21. Ibarra, R. U., Edwards, J. S. & Palsson, B. O. Evolution towards predicted optimal growth in *Escherichia coli K-12. Nature* 420, 186-189 (2002).

22. Edwards, J. S., Ramakrishna, R. & Palsson, B. O. Characterizing the metabolic phenotype: A phenotype phase plane analysis. *Biotechnol Bioeng* 77, 27-36 (2002).

23. Edwards, J. S., Covert, M. W. & Palsson, B. O. Metabolic Modeling of Microbes: the Flux-Balance Approach. *Environ Microbiol* 4, 133-140 (2002).

24. Merritt, J., DiTonno, J. R., Mitra, R. D., Church, G. M. & Edwards, J. S. Functional characterization of mutant yeast PGK1 within the context of the whole cell. *Nucleic Acids Res* 31, e84 (2003).

25. Lall, R., Gao, G., Dhurjati, P. & Edwards, J. S. MRAD: Metabolic Reaction Analysis Database – An Entity-Relationship Approach. *J Mol Microbiol Biotechnol* 6, 12-18 (2003).

26. Kauffman, K. J., Prakash, P. & Edwards, J. S. Advances in Flux Balance Analysis. *Current Opinion in Biotechnology* 14, 491-496 (2003).

27. Ibarra, R. U., Fu, P., Palsson, B. O., DiTonno, J. R. & Edwards, J. S. Quantitative Analysis of E. coli Metabolic Phenotypes within the Context of Phenotypic Phase Planes. *J Mol Microbiol Biotechnol* 6, 101-108 (2003).

28. Edwards, J. S. & Kauffman, K. J. Biochemical Engineering in the 21st Century. *Curr Opin Biotechnol* 14, 451-453 (2003).

29. Edwards, J. S. & Battista, J. R. Using DNA microarray data to understand the ionizing radiation resistance of *Deinococcus radiodurans. Trends Biotechnol* 21, 381-382 (2003).

30. Butz, J., Wickstrom, E. & Edwards, J. S. Characterization of Mutations and LOH of p53 and K-ras2 in Pancreatic Cancer Cell Lines by Immobilized PCR. *BMC Biotechnol* 3, 11 (2003).

31. Altenbaugh, R. E., Kauffman, K. J. & Edwards, J. S. Suitability and utility of computational analysis tools: characterization of erythrocyte parameter variation. *Pac Symp Biocomput*, 104-15 (2003).

32. Ruhela, A., Verma, M., Edwards, J. S., Bhat, P. J., Bhartiya, S. & Venkatesh, K. V. Autoregulation of Regulatory Proteins is Key for Dynamic Operation of GAL Switch in *Saccharomyces cerevisiae. FEBS Lett* 576, 119-126 (2004).

33. Patel, S., Venkatesh, K. V. & Edwards, J. S. An integrated mechanistic model for transcription-coupled nucleotide excision repair. *DNA Repair* 3, 343-348 (2004).

34. Patel, S. & Edwards, J. S. RecA mediated initial alignment of homologous DNA molecules displays apparent first order kinetics with little effect of heterology. *DNA Repair* 3, 61-65 (2004).

35. Mutalik, V. K., Singh, A. P., Edwards, J. S. & Venkatesh, K. V. Equilibrium analysis of allosteric interactions shows zero-order effects. *Cell Biochemistry and Biophysics* 41, 179-192 (2004).

36. Mutalik, V. K., Singh, A. P., Edwards, J. S. & Venkatesh, K. V. Robust global sensitivity in multiple enzyme cascade system explains how the downstream cascade structure may remain unaffected by cross-talk. *FEBS Letters* 558, 79-84 (2004).

37. Mikkilineni, V., Mitra, R. D., DiTonno, J. R., Merritt, J., Church, G. M., Ogunnaike, B. A. & Edwards, J. S. Digital Quantitative Measurements of Gene Expression. *Biotech Bioeng* 86, 117-124 (2004).

38. Merritt, J. & Edwards, J. S. Assaying gene function by growth competition experiment. *Metab Eng* 6, 212-219 (2004).

39. Mayawala, K., Gelmi, C. A. & Edwards, J. S. MAPK cascade possesses decoupled controllability of signal amplification and duration. *Biophys J* 87, L01-2 (2004).

40. Goodkind, J. R. & Edwards, J. S. Gene Expression Measurement Technologies: Innovations and Ethical Considerations. *Computers & Chemical Engineering* In Press (2004).

41. Butz, J., Yan, H., Mikkilineni, V. & Edwards, J. S. Detection of allelic variations of human gene expression by polymerase colonies. *BMC Genetics* 5 (2004).

42. Butz, J., Goodwin, K. & Edwards, J. S. Detecting changes in the relative expression of K-ras2 splice variants using polymerase colonies. *Biotechnol Prog* 20, 1836-1839 (2004).

43. Merritt, J., Butz, J. A., Ogunnaike, B. A. & Edwards, J. S. Parallel analysis of human glucose-6-phosphate dehydrogenase single-nucleotide mutants via functional complementation in S. cerevisiae using polymerase colonies. *Biotech Bioeng* 92, 519-531 (2005).

44. Mayawala, K., Vlachos, D. G. & Edwards, J. S. Heterogeneities in EGF receptor density at the cell surface can lead to concave up scatchard plot of EGF binding. *FEBS Lett* 579, 3043-7 (2005).

45. Mayawala, K., Valchos, D. G. & Edwards, J. S. Computational modeling reveals molecular details of epidermal growth factor binding. *BMC Cell Biol* 6, 41 (2005).

46. Gadkar, K. G., Doyle III, F. J., Edwards, J. S. & Mahadevan, R. Estimating optimal profiles of genetic alterations using constraint-based models. *Biotechnol Bioeng* 89, 243-51 (2005).

47. Chatterjee, A., Mayawala, K., Edwards, J. S. & Vlachos, D. G. Time accelerated Monte Carlo simulations of biological networks using the binomial {tau}-leap method. *Bioinformatics* (2005).

48. Mayawala, K., Vlachos, D. G. & Edwards, J. S. Spatial modeling of dimerization reaction dynamics in the plasma membrane: Monte Carlo vs. continuum differential equations. *Biophys Chem* In Press (2006).

C. Research Support

Ongoing Research Support

Edwards (PI)   09/01/05 – 08/31/07
Louisiana State University (Subcontract with U.S. Department of Energy DE-GF02-01ER63151)
Identifying the Proteins that Mediate the Ionizing Radiation Resistance of Deinococcus Radiodurans R1
The goal of this project is to characterize the mechanisms of ionizing radiation resistance in deinococcus radiodurans R1.
Role: PI

NIH/NIAID   Wilson (PI)   09/15/05 – 06/30/08
MSM Mapping and Modeling ErbB Receptor Membrane Topography
Overall goal of the project is to collect quantitative experimental data on the spatial heterogeneity of ErbB receptor expression in endometrial cancer cell lines and within endometrial cancer tissue; and to develop multiscale models that can analyze and integrate these data.
Role: Co-PI

Leukemia Lymphoma Society   Willman, (PI)   10/01/05 – 09/30/10
Specialized Center of Research in Acute Leukemia: comprehensive molecular technologies for improved risk classification and therapy. Project 4 dynamica analysis of signaling networks in leukemia.
Overall goal of the project is to use sophisticated biochemical, imaging, and computational modeling tools to develop and model cell signaling networks and pathways.
Role: Co-Investigator

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Palsson, Bernhard   Customer No.: 41552
Appl. No. : 09/923,870   Confirmation No.: 1729
Filed   : August 06, 2001
Title   : METHODS FOR IDENTIFYING
               DRUG TARGETS BASED ON
               GENOMIC SEQUENCE DATA

Grp./A.U. : 1647
Examiner: : Allen, Marianne P.

DECLARATION UNDER 37 C.F.R. §1.132

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jeremy S. Edwards, Ph.D., declare as follows:

1)   I am currently an Assistant Professor at the Department of Molecular Genetics and Microbiology at the University of New Mexico Health Science Center, Albuquerque, New Mexico. I previously held the Outstanding Junior Faculty Chaired Professorship position in Chemical Engineering at the University of Delaware.

2)   I obtained a Bachelors of Science majoring in Mechanical Engineering in 1995 from the University of Texas, Arlington and my Ph.D. in Bioengineering from the University of California, San Diego, in 1999, where I did my thesis work in Dr. Bernhard Palsson's laboratory. I also completed a post-doctoral fellowship at Harvard Medical School in 2000. I have authored or co-authored numerous papers in the areas of genomics and bioinformatics including *in silico* organism models, spatial-temporal modeling of signaling networks and functional genomics tool development. My curriculum vitae and a list of publications is attached as Exhibit 1.

3)   I have read the application entitled Methods for Identifying Drug Targets Based on Genomic Sequence Data, having U.S. patent application serial no. 09/923,870. Specifically, I understand that the application describes and claims computer methods for producing a genome specific stoichiometric matrix and computer methods for producing an *in silico* representation of a microbe. The methods rely, in part, on the identification and inclusion of metabolic reactions into an *in silico* model of an organism.

4)   I have read the Office Action mailed December 22, 2006, issued in connection with the above-identified application. I understand that claims 49-54, 56-62 and 64-65 have been rejected for lacking enablement in the application. In particular, I understand that the Examiner asserts that the application fails to provide adequate guidance as to how to evaluate sufficiency of the number of genes in an *in silico* representation of a microbe.

5)   My understanding from reading the application is that it provides sufficient guidance to one skilled in the field of *in silico* modeling for assessing sufficiency of the number of metabolic genes to include in an *in silico* representation. Those skilled in the field of *in silico* modeling understand that a computer model is sufficient when it is consistent with known results of the thing or organism being modeled. The application adequately provides this guidance to one skilled in this field of *in silico* modeling.

6)   The application sets forth guidance on such a comparison when it explains "[t]he growth associated maintenance requirements are determined by fitting the model results to the experimentally determined points in the growth rate versus glucose rate plot" (page 8, lines 5-7; emphasis added). This guidance is further emphasized by a comparison of *in silico* and *in vivo* results where the application explicitly describes "we can call upon the wealth of data on overall metabolic behavior and detailed biochemical information about the *in vivo* genotype to which we can compare the behavior of the *in silico* strain (page 14, last paragraph, lines 6-8; emphasis added).

7)   The above descriptions adequately instruct one skilled in the art of *in silico* modeling that the number of genes to include in an *in silico* representation is an amount sufficient for the model to show consistencies with known behavior of the actual organism. These descriptions further instruct one skilled in the art of *in silico* modeling that such
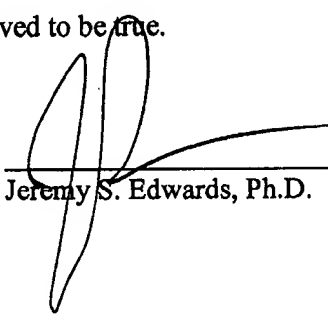
sufficiency of the number of metabolic genes to include in an *in silico* representation can readily be determined by comparison with results obtained *in vivo*.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true.

Date: _____   By: _____
                                        Jeremy S. Edwards, Ph.D.

3

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME Jeremy S Edwards	POSITION TITLE Assistant Professor
eRA COMMONS USER NAME jedwards	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Texas, Arlington	B.S.	1995	Mech Eng
University of California, San Diego	M.S.	1997	Bioengineering
University of California, San Diego	Ph.D.	1999	Bioengineering

A. Positions and Honors

Positions and Employment
1999 - 2000	Postdoctoral Fellow, Department of Genetics, Harvard Medical School
1999 - 2005	Assistant Professor, Chemical Engineering, University of Delaware
2005-	Assistant Professor, Department of Molecular Genetics and Microbiology, University of New Mexico Health Sciences Center
2005-	Member, Cancer Research and Treatment Center, University of New Mexico Health Sciences Center
2005	Assistant Professor, Department of Chemical Engineering, University of New Mexico

Honors, Awards and Professional Memberships
1995	University of Texas, Arlington, Summa Cum Laude
2003-2004	Outstanding Named Junior Professor of Engineering

Member, American Association for the Advancement of Science (AAAS)
Member, American Society for Microbiology (ASM)
Member, American Institute or Chemical Engineers (AIChE)

B. Selected peer-reviewed publications
1. Edwards, J. S. & Palsson, B. O. How will bioinformatics influence metabolic engineering? *Biotechnology and Bioengineering* 58, 162-169 (1998).
2. Schilling, C. H., Edwards, J. S. & Palsson, B. O. Towards metabolic phenomics: Analysis of genomic data using flux balances. *Biotechnology Progress* 15, 288-95 (1999).
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4. Edwards, J. S. & Palsson, B. O. Systems Properties of the *Haemophilus influenzae* Rd Metabolic Genotype. *Journal of Biological Chemistry* 274, 17410-17416 (1999).
5. Schilling, C. H., Edwards, J. S., Letscher, D. & Palsson, B. O. Combining pathway analysis with flux balance analysis for the comprehensive study of metabolic systems. *Biotechnology and Bioengineering* 71, 286-306 (2000).
6. Edwards, J. S., Schilling, C. H., Covert, M. W., Smith, S. J. & Palsson, B. O. in *Encyclopedia of Microbiology* (ed. Lederberg, J.) (American Society for Microbiology, 2000).
7. Edwards, J. S. & Palsson, B. O. Metabolic flux balance analysis and the *in silico* analysis of *Escherichia coli* K-12 gene deletions. *BMC Bioinformatics* 1, 1 (2000).
8. Edwards, J. S. & Palsson, B. O. Robustness Analysis of the *Escherichia coli* metabolic network. *Biotechnol Prog* 16, 927-939 (2000).
9. Edwards, J. S. & Palsson, B. O. The *Escherichia coli* MG1655 in silico metabolic genotype: its definition, characteristics, and capabilities. *Proc Natl Acad Sci U S A* 97, 5528-33 (2000).
10. Edwards, J. S. & Palsson, B. O. Multiple steady states in kinetic models of red cell metabolism. *J Theor Biol* 207, 125-127 (2000).

11. Tchieu, J. H., Norris, V., Edwards, J. S. & Saier, M. H., Jr. The complete phosphotranferase system in *Escherichia coli. J Mol Microbiol Biotechnol* 3, 329-46. (2001).

12. Ramakrishna, R., Edwards, J. S., McCulloch, A. & Palsson, B. O. Flux-balance analysis of mitochondrial energy metabolism: consequences of systemic stoichiometric constraints. *Am J Physiol Regul Integr Comp Physiol* 280, R695-R704 (2001).

13. Jamshidi, N., Edwards, J. S., Fahland, T., Church, G. M. & Palsson, B. O. Dynamic simulation of the human red blood cell metabolic network. *Bioinformatics* 17, 286-7. (2001).

14. Edwards, J. S., Ibarra, R. U. & Palsson, B. O. *In silico* predictions of *Escherichia coli* metabolic capabilities are consistent with experimental data. *Nat Biotechnol* 19, 125-130 (2001).

15. Covert, M. W., Schilling, C. H., Famili, I., Edwards, J. S., Goryanin, I. I., Selkov, E. & Palsson, B. O. Metabolic Modeling of Microbial Strains *in silico. Trends Biochem Sci* 26, 179-86 (2001).

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C. Research Support

Ongoing Research Support